INFLAMMATION

THE THROMBO-INFLAMMATION AXIS AS PREDICTOR OF TOXICITY IN PATIENTS TREATED WITH CAR-T CELLS

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Introduction. CAR-T cell therapy has transformed hematologic malignancies treatment. Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are its major toxicities. Thromboinflammation, involving neutrophil extracellular traps (NETs) and extracellular vesicles (EVs), remains unexplored in this setting.

Aim. To characterize thromboinflammatory-related biomarkers and EVs of distinct cellular origin, assess temporal dynamics and evaluate their potential as predictors of toxicity after CAR-T therapy.

Methods. Prospective study in adult patients with hematologic malignancies treated with anti-CD19 or anti-BCMA CAR-T at two centres. Samples were collected before lymphodepletion, at infusion, at 48 hours and 14 days post-infusion. Elastase, Double strand Circulating DNA (dsDNAc) and P-selectin were quantified using ELISA and fluorescence-based assays. EVs of red blood cell, platelet, endothelial, and myeloid origin were characterised by flow cytometry. Associations with the occurrence of ICANS, clinically significant CRS (grade ≥ 2) and major or clinically relevant bleeding events within 30 days post-infusion were analysed.

Results. Sixty-two patients were included (median age 62 years; 65% male): 29 with multiple myeloma and 33 with B-cell malignancies. Clinically significant CRS occurred in 20 patients (31%), and ICANS in 24 (26%), with median onset at days 3 and 6, respectively. Eight major or clinically relevant bleeding events (13%) were observed, all but one after day 14. Only one thrombotic event (1.6%) occurred. Elastase and P-selectin levels decreased after lymphodepletion with partial recovery, while dsDNAc levels remained stable. All EV subtypes declined significantly over time. No biomarker, including EVs, was associated with clinically relevant CRS. In univariate analysis, dsDNAc levels were significantly higher in patients who developed ICANS. DsDNAc at 48 hours remained independently associated with ICANS (OR 24, 95% CI 1.01–570; p=0.049), yielding an AUC of 0.78. At 48 hours, platelet-derived EVs (CD41/61+) and P-selectin levels were associated with bleeding risk, although not independently of platelet count.

Conclusions. Early elevation of circulating dsDNAc may serve as an independent predictor of ICANS and could help in the risk stratification and monitoring of patients undergoing CAR-T cell therapy.

Figure 1. ROC curve from the 48-hour multivariable analysis (dependent variable: ICANS; independent variables: dsDNAc and CRP)